REMARKS

Applicants have cancelled Claims 1-3, and 7-10 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Claim 4 has been rewritten in independent form and Claims 5 and 17 have been amended to depend from Claim 4. Applicants have amended Claims 4, 5, 6 and 14 to delete elements (a)-(d). Claims 4 and 5 are amended to delete the portion of the claim "or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively." Claims 4-6 and 14 are amended to delete "wherein said extracellular domain is amino acids 18-81 or 146-163 of SEQ ID NO:120." Claim 14 is amended to include "or a complement thereof" to amended elements (a)-(c), and the following text "wherein said isolated nucleic acid molecule is suitable for use as a PCR primer, or probe; and wherein said isolated nucleic acid is at least about 20 nucleotides in length." Claim 16 is amended to read "at least about 50 nucleotides in length." Claim 19 is amended to read "An isolated host cell." New Claims 21-31 have been added.

Applicants submit that no new matter has been added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendments to Claim 14 can be found, for example, at paragraphs [0012], [0317], and [0327] of the specification. Support for the amendment to Claim 16 and new Claims 21-25 can be found, for example, at paragraph [0012]. Support for new Claims 26-31 can be found, for example, in the claims as originally filed, and paragraphs [0227] and [0317].

Applicants thank the Examiner for his review of the instant application and withdrawing the objection to the title and specification, acceptance of the copy of the sequence listing, acknowledgement of Applicants' request for correction of inventorship, and acknowledgment of the BLAST searches. Applicants acknowledge the Examiner's withdrawal of the rejection of Claims 1-14 and 16-20 under 35 U.S.C. § 112, second paragraph, as being indefinite, the rejection of Claims 1-6, 9, 10 and 14 under 35 U.S.C. § 112, first paragraph, written description, with respect to recitation of "extracellular domain" and "signal peptide," and the rejection of

Claim 6 under 35 U.S.C. § 112, first paragraph, scope of enablement, with respect to recitation of "extracellular domain" and "signal peptide."

Applicants acknowledge that the Examiner has withdrawn the rejection of Claims 1-7, 9 and 11 under 35 U.S.C. § 102(b) as anticipated by Keen *et al.* However, Applicants note that the Examiner also rejected Claims 12 and 13 under 35 U.S.C. § 102(b) as anticipated by Keen. *See Office Action dated 9/21/2004* at page 17, ¶ 9a. Applicants ask that the Examiner confirm that the rejection is also withdrawn with respect to Claims 12 and 13.

Applicants also acknowledge that the Examiner has withdrawn the rejection of Claims 8, 10, 12 and 13 under 35 U.S.C. § 103(a) as unpatentable over Keen *et al.* in light of Jacobs. However, Applicants note that the Examiner originally rejected Claims 14-20 under 35 U.S.C. § 103(a) as unpatentable over Keen *et al.* in light of Jacobs. *See Office Action dated 9/21/2004* at page 18, ¶ 10a. Applicants ask that the Examiner confirm that the rejection is also withdrawn with respect to Claims 14-20.

For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 4-6, 11-14, and 16-31 are presented for examination.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the filing date of the present application, May 8, 2002, is considered the priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/105002 filed 10/20/1998.

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 119 and 120 were first

disclosed in US Provisional Application 60/105002 filed 10/20/1998 in Figures 2A-C and 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 1-14, and 16-20 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO asserts that "[g]iven the increase in expressed message for PRO1573 ..., and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a higher cDNA expression would correlate with increased polypeptide levels." Office Action at 6. The PTO relies on Haynes *et al.*, Hu *et al.* and Chen *et al.* for the propositions that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels and that polypeptide levels cannot be accurately predicted from mRNA levels. Office Action at 5-6. The PTO argues that further research is required to determine the role of PRO1573 in cancer, making the asserted utility not substantial. Office Action at 6. The PTO also states that declarations submitted with Applicants' previous response are insufficient to overcome the rejection.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge**

> **in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved.

1. Applicants assert they have provided reliable evidence that mRNA for the PRO1573 polypeptide is expressed at least two-fold higher in esophageal and lung tumor tissue, and normal

kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively, and therefore the claimed nucleic acids are useful as diagnostic tools. Applicants are not asserting that the claimed nucleic acids will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers;

2. Applicants submit that it is not necessary to know what role the PRO1573 gene plays in cancer to use its differential expression as a diagnostic tool;

3. It is not required to prove that the PRO1573 polypeptide is also differentially expressed in certain tumors to establish the utility of the claimed nucleic acids.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, stating that specification does not teach what is the normal level of expression, does not indicate how high or low the expression level is compared to for example, normal esophagus or skin, and does not provide a statistical correlation to the level of expression;

2. The PTO cites Hu *et al.* to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue;

3. The PTO cites Haynes *et al.* and Chen *et al.* to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1573 cDNA expression supports a role for the peptide in cancerous tissue.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. In addition, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi

in support of these data. Second, Hu *et al.* is not contrary to Applicants' asserted utility and does not support the PTO's position. Finally, Applicants submit that given the well-established correlation between a change in the level of mRNA and a corresponding change in the levels of the encoded protein, the PRO1573 protein is likely differentially expressed in certain tumors. However, utility for the pending claims does not rely on whether the encoded polypeptide is overexpressed, and as such whether or not increased levels of PRO1573 mRNA correlate with increased levels of PRO1573 protein is not presently an issue.

Applicants have established that the Gene Encoding the PRO1573 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's previous argument that the evidence of differential expression of the gene encoding the PRO1573 polypeptide in esophageal, lung, kidney, and skin tissues is insufficient because the specification does not teach what is the normal level of expression, does not indicate how high or low the expression level is compared to for example, normal lung; and does not provide a statistical correlation to the level of expression. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1573 gene is differentially expressed in esophageal, lung, kidney, and skin tumors compared to their normal tissue counterparts.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1573 was more highly expressed in esophageal and lung tumor tissue, and normal kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1573 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants previously submitted as Exhibit 2 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-14, and 16-20, offering two arguments. First, the PTO argues that "there is no evidentiary art that would corroborate for example, that 'any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor

tissue and the counterpart normal tissue.'" Office Action at 14 (quoting first Grimaldi Declaration).

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *See in re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In addition, Applicants provide herewith as Exhibit 1 a copy of page 122 of the 2002-2003 New England Biolabs catalog. Exhibit 1 shows DNA size markers of differing lengths run on an agarose gel. The column on the left provides the mass of each marker in nanograms and the column on the right provides the length of the marker. It is apparent that the band intensity of markers having mass differences of two-fold are readily distinguishable by eye (*see e.g.*, the difference in band intensities of the 0.1kb fragment present at 61ng and the 0.5kb marker present at 124ng). Accordingly, Applicants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences.

The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the nucleic acids of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

The PTO also cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for its assertion the literature cautions researchers from drawing conclusions based on small changes in

transcript expression levels between normal and cancerous tissue. The PTO states that Hu teaches that not all genes with increased expression in cancer have a known or published role in cancer. Office Action at 6, 14.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease

and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Finally, the PTO also argues that further research needs to be done to determine if the increase or decrease in PRO1573 DNA supports a role for the peptide in cancerous tissue and that such a role has not been suggested by the instant disclosure. (See Office Action at 6-7).

Applicants submit that a lack of known role for PRO1573 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1573 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a

particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No. 6,162,604 submitted herewith as Exhibits 2-4), even though they may or may not cause the disease itself. Similarly, the present nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1573 cDNA between esophageal and lung tumor tissue, and normal kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively. Therefore, it follows that expression levels of the PRO1573 gene can be used to distinguish normal esophageal, lung, kidney, and skin tissue from esophageal, lung, kidney, and melanoma tumors. The PTO has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed nucleic acids as diagnostic tools for cancer, particularly esophageal lung, kidney, and melanoma tumors.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)) and Chen *et al.* (Mol. and Cell. Proteomics, 1:304-313 (2002)) as support for its argument that "polypeptide levels cannot be accurately predicted from mRNA levels." Office Action at 17-18. Because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression is not presently at issue. Thus, the Haynes and Chen references are not relevant. However, even if this issue were important for the utility of the claimed nucleic acids, Haynes and Chen do not support the PTO's position.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the

corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 5 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did <u>not</u> say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the <u>same</u> gene leads to a increase or decrease for the corresponding protein. Haynes did <u>not</u> study this issue and says absolutely nothing about it.

Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation

between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to

detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 6). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased

polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 7), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 6) and (4th ed. 2002) (submitted herewith as Exhibit 7)). Figure 9-2 of Exhibit 6 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 6 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 6 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 6 at 453 (emphasis added). Thus, as

established in Exhibit 6, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 7, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 7 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 7 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 7 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 7 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 8) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 9. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 9 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 9 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors

state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 9 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 10, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1573 mRNA is more highly expressed in esophageal and lung tumor tissue, and normal kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively, the PRO1573 polypeptide will also be more highly expressed in esophageal and lung tumor tissue, and normal kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively. However, as stated above, because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression is not presently at issue.

The References cited by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

There is nothing in the cited references which cast any doubt on the Applicants' asserted utility. As stated previously, the Sen *et al.* and Pennica *et al.* references are not relevant because Example 18 reports gene expression data, not gene amplification data. Similarly, Hu *et al.*, Haynes *et al.* and Chen *et al.* are also not sufficient to satisfy the PTO's burden of offering evidence that a person of skill in the art would have a reasonable doubt that a gene differentially expressed in certain tumors can be used as a diagnostic tool, since none of these references address this issue. Given the lack of support for the PTO's position, and the supporting evidence provided by the Applicants for their position, one of skill in the art would be more likely than not

to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly esophageal, lung, kidney, and melanoma tumors.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed nucleic acids related to PRO1573. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1573 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that that the gene for the PRO1573 polypeptide is expressed at least two-fold higher in esophageal and lung tumor tissue, and normal kidney and skin tissue compared to normal esophageal and lung tissue, and kidney and melanoma tumor tissue, respectively. These data are strong evidence that the PRO1573 gene is associated with esophageal, lung, kidney, and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1573 gene with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal, lung, kidney, and melanoma tumors, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted three arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that the increase in gene amplification of PRO1573 would correlate with increased mRNA or polypeptide levels: (1) the PTO has challenged the reliability of the evidence reported in Example 18; (2) the PTO cites Hu *et al.* and to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and, (3) the PTO cites Haynes *et al.* and Chen *et al.* for support for the assertion that mRNA levels are not

predictive of protein levels. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1573 cDNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration. Therefore, Applicants have established a basis for the use of the claimed nucleic acids as diagnostic tools, particularly for esophageal, lung, kidney, and melanoma tumors. Second, Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1573 nucleic acids in certain tumors in order to use them as diagnostic tools for cancer. Third, Applicants state that whether the encoded polypeptide is also differentially expressed in certain tumors is currently not at issue in this application.

Applicants have previously shown that the Sen *et al.* and Pennica *et al.* references are irrelevant to the utility of the claimed nucleic acids. Applicants have also shown that the Hu *et al.,* Haynes *et al.* and Chen *et al.* references are not contrary to Applicants' asserted utility. Taken together, these references do not satisfy the PTO's burden of offering evidence to prove that one of skill in the art would reasonably doubt the asserted utility.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acid because the PRO1573 gene and polypeptide are differentially expressed in certain tumors compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of nucleic acids.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic tool. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack

> utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids as diagnostic tools as set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 1-14, and 16-20 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. The PTO also states that even if Applicants establish utility for SEQ ID NO:119 or fragments of such as hybridization probes, they are not enabled for polynucleotides that are 80-99% identical to SEQ ID NO:119 or which encode a polypeptide which is 80-99% identical to the protein of SEQ ID NO:120, or polynucleotides which hybridize to any of the above "because there is no structural or functional information provided in the specification." Office Action at 19. The PTO argues that there is no way of knowing which, if any variants would have the same property of higher expression in the specific tissue.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As amended, the pending claims are to nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the recited sequences and are "wherein said isolated nucleic acid is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney

tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively" or "hybridizes to the complement of a nucleic acid of SEQ ID NO:119" under the specified stringent conditions. Other claimed nucleic acids are those which hybridize to the recited sequences under stringent conditions. The pending claims are not defined by the polypeptide sequence they encode.

Applicants submit that the claimed nucleic acids are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences related to SEQ ID NO:119. Likewise, Applicants have disclosed how to determine if the claimed nucleic acids are differentially expressed in esophageal, lung, kidney, or melanoma tissues compared to their normal counterparts (*see, e.g.,* Example 18 beginning at paragraph [0529] of the specification). Finally, it is well-known in the art how to determine if a nucleic acid hybridizes to the disclosed sequences under the specified stringent conditions. Thus, one of skill in the art would know how to make the claimed nucleic acids.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1573 gene is differentially expressed in esophageal, lung, kidney, and melanoma tumors. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed nucleic acids as diagnostic tools. For example, nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences and are "more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively" can be used as diagnostic tools since the claimed nucleic acids are themselves differentially expressed in certain tumors. A claimed nucleic acid which has at least 95% or 99% sequence identity to the disclosed sequences and "hybridizes to the complement of a nucleic acid of SEQ ID NO:119," or which hybridizes to the disclosed sequences under the specified stringent conditions can be used as a hybridization probe to detect the expression of the PRO1573 gene, making it useful as a diagnostic tool. Given the skill in the art and the disclosure of how to make and use the claimed nucleic acids, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The rejection of Claims 1-5, and 16-20 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement is maintained for the reasons set forth in the previous Office Action. Briefly, the PTO asserts the "Applicants were not in possession of all or a significant number polypeptides that have 80-99% homology to SEQ ID NO: 120 and still retain the function of SEQ ID NO: 120." Office Action at 20-21.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience.

Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:119, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:119, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203356, with the functional recitation as amended: "wherein said isolated nucleic acid is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO:119" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:119, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:119, the full-length coding sequence of the cDNA deposited under ATCC accession number 203356, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they

hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument the claimed sequences do not possess "any particular conserved structure, or other disclosed distinguishing feature." (August 3, 2004 Office Action at 7). The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO:119, such that they hybridize to SEQ ID NO:119 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO:119 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the

specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:119 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in esophageal tumor tissue, lung tumor tissue, normal kidney tissue, or normal skin tissue compared to normal esophageal tissue, normal lung tissue, kidney tumor tissue or melanoma tumor tissue, respectively" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants, and the applicant would not know if a particular variant possessed the requisite catalytic activity until the variant was tested.

Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in esophageal or melanoma tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 11-16.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:119,

by specifying the high stringency conditions under which hybridization occurs, and by describing the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 18, 2005

By: _____
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

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063005